Synthesis of Some Novel Functionalized Monoazatricyclic Ring Systems via Intramolecular Cycloaddition of *N*-(Bicycloalkenyl)nitrones[1]

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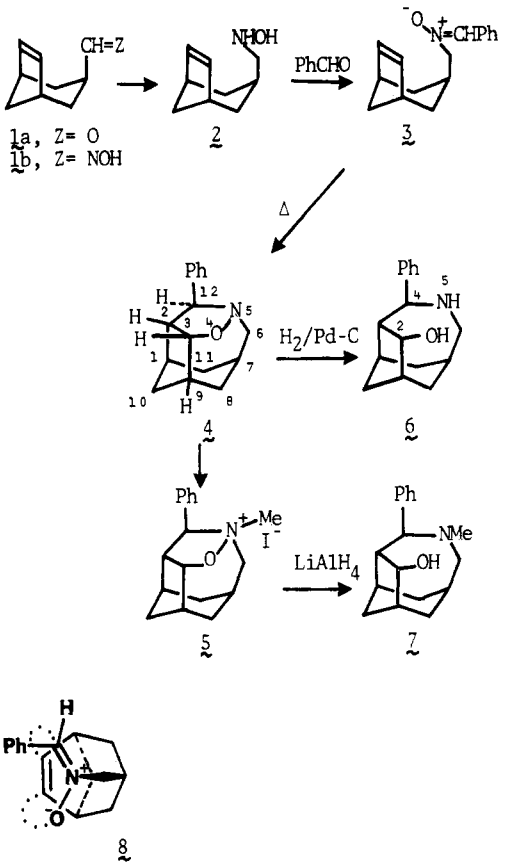
The intramolecular cycloaddition of *C*-phenyl-*N*-(*endo*-bicyclo[3.2.1]oct-6-en-3-ylmethyl)nitrone (**3**) generated in situ from the corresponding hydroxylamine and benzaldehyde gave the adduct **4** in a high yield. Reductive cleavage of **4** afforded 2-*endo*-hydroxy-4-*endo*-phenyl-5-azatricyclo[5.3.1.$0^{3,9}$]undecane (**6**). The intramolecular cycloadditions of unsymmetrical *N*-(*endo*-bicyclo[2.2.1]hept-5-en-2-ylmethyl)nitrones (**11a,b**) and *N*-(*endo*-bicyclo[2.2.2]oct-5-en-2-ylmethyl)nitrones (**23a,b**) occurred regiospecifically to afford the adducts **12a,b** and **24a,b**, respectively. Reductive cleavage of these adducts provided a convenient route to functionalized 5-azatricyclo-[5.2.1.$0^{3,8}$]decanes (**15a,b, 16, 17**) and 5-azatricyclo[5.3.1.$0^{3,8}$]undecanes (**27a,b, 28, 29**), respectively. The regiochemical and stereochemical assignments of **12a** and **24a** were proven by X-ray analysis of the methiodides **14a** and **26a**, respectively.

Recently we have reported a convenient stereospecific synthesis of amino alcohol derivatives of noradamantane, protoadamantane, and adamantane based on the intramolecular 1,3-dipolar cycloaddition of appropriate *C*-(bicycloalkenyl)nitrones.[2] This is an example of our efforts of pursuing attractive synthetic routes for functionalized carbo- and heterocyclic cage series.[3,4] In this paper, we report on a convenient synthesis of some novel functionalyzed monoazatricyclic ring systems based on *N*-(bicycloalkenyl)nitrones.[5-8]

Results and Discussion

Synthesis of 2-*endo*-Hydroxy-4-*endo*-phenyl-5-azatricyclo[5.3.1.$0^{3,9}$]undecane (6) and Related Derivatives via *C*-Phenyl-*N*-(*endo*-bicyclo[3.2.1]oct-6-en-3-ylmethyl)nitrone (3). The *N*-(bicycloalkenyl)-nitrone **3**, containing a symmetrical olefin, was generated in situ by stirring benzaldehyde and *N*-(*endo*-bicyclo-[3.2.1]oct-6-en-3-ylmethyl)hydroxylamine (**2**) prepared from the aldehyde **1a**[9] via oxime **1b**. The intramolecular cycloaddition of the nitrone **3** occurred smoothly upon heating in xylene under reflux to afford 12-*exo*-phenyl-4-oxa-5-azatetracyclo[5.3.1.$1^{2,5}$.$0^{3,9}$]dodecane[10] (**4**) in 95% yield (Scheme I). The given structure and stereochemistry were corroborated by appearance of characteristic ^{1}H

Scheme I



(1) Synthesis of Adamantane Derivatives. 77. Part 76: Eguchi, S.; Wakata, Y.; Sasaki, T. *J. Chem. Res.*, in press.

(2) Sasaki, T.; Eguchi, S.; Suzuki, T. *J. Org. Chem.* **1982**, *47*, 5250.

(3) For example, see: Sasaki, T.; Eguchi, S.; Okano, T. *J. Org. Chem.* **1981**, *46*, 4474.

(4) (a) For a recent review on adamantane and related chemistry, see: Fort, R. C., Jr. In "Studies in Organic Chemistry"; Gassmann, P. G., Ed.; Marcel Dekker: New York, 1976; Vol. 5. (b) For recent reviews on heterotricycles and related systems, see: Ganter, C. *Top. Curr. Chem.* **1976**, *67*, 15. (c) Sasaki, T. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Ed.; Academic Press: New York, 1982; Vol. 30, pp 79–126.

(5) For recent reviews on intramolecular 1,3-dipolar cycloadditions, see: (a) Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123. (b) Oppolzer, W. *Ibid.* **1977**, *16*, 10.

(6) For general reviews and some leading references on nitrone cycloadditions, see: (a) Huisgenm R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565, 633. (b) Hamer, J.; Macluso, A. *Chem. Rev.* **1964**, *64*, 473. (c) Black, D. St. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205. (d) Freeman, J. P. *Chem. Rev.* **1983**, *83*, 241. (e) Padwa, A.; Fisera, L.; Koehler, K. F.; Rodriguez, A.; Wong, G. S. *J. Org. Chem.* **1984**, *49*, 276. (f) Ashburn, S. P.; Coates, R. M. *Ibid.* **1984**, *49*, 3127.

(7) For other examples of nitrone-based synthesis of functionalized bicyclic and azabicyclic systems, see: (a) LeBel, N. A.; Ojha, N. D.; Menke, J. R.; Newland, R. *J. Org. Chem.* **1972**, *37*, 2896. (b) LeBel, N. A.; Hwang, D. "Organic Syntheses"; Wiley: New York, 1978; Vol. 58, p 106. (c) Baily, J. T.; Berger, I.; Friary, R.; Puar, M. S. *J. Org. Chem.* **1982**, *47*, 857. (d) Confalone, P. N.; Huie, E. M. *J. Org. Chem.* **1983**, *48*, 2994.

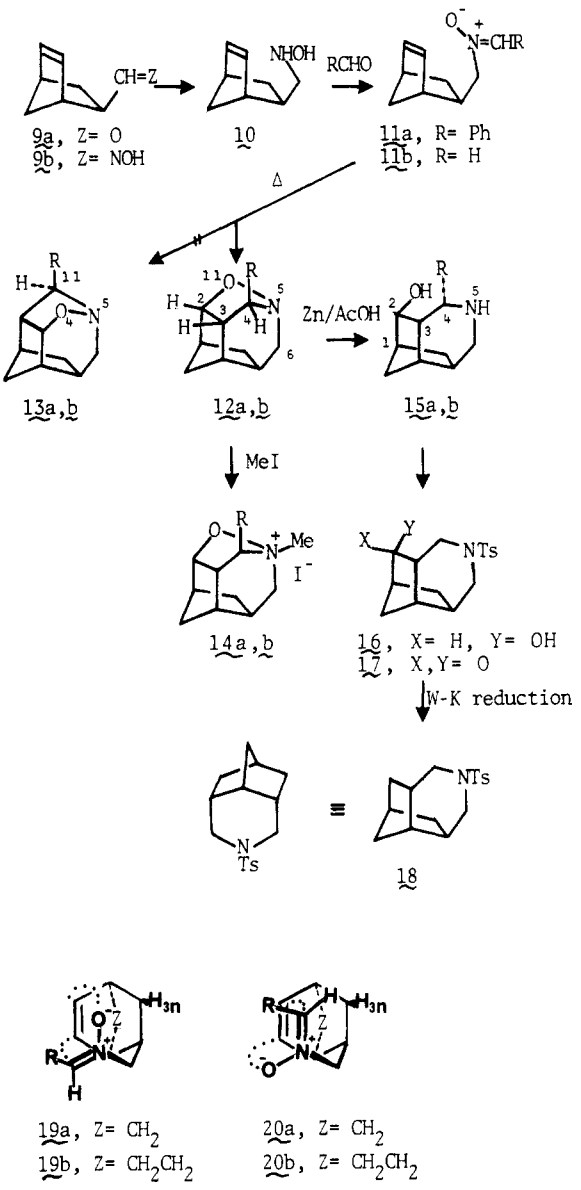
(8) For reviews on nitrone-based synthesis of alkaloids, see: (a) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (b) Oppolzer, W. *Pure Appl. Chem.* **1981**, *53*, 1181.

(9) Garratt, P. J.; White, J. F. *J. Org. Chem.* **1977**, *42*, 1733 and references cited therein.

(10) In this paper, a substituent is designated conventionally as exo if it is oriented toward the smaller ring of a polycyclic skeleton and endo if it faces the larger ring.

0022-3263/85/1950-1895$01.50/0

Scheme II



NMR signals at δ 4.9 (dd, J = 9.0 and 6.0 Hz, H_3) and 4.20 (s, H_{12endo}) and ^{13}C NMR signals at δ 89.1, 68.1, and 61.2 (each d and for 1 C) due to isooxazolidine ring carbons.[11-14] The exclusive formation of the exo isomer **4** is rationalized based on the transition state **8** which involves the *anti*-nitrone and is apparently more favorable than that for the *syn*-nitrone as suggested by examination of molecular models.[15,16] Treatment of **4** with methyl iodide gave the methiodide **5** in a good yield. Catalytic reduction (Pd-C) of **4** and $LiAlH_4$ reduction of **5** afforded new cage amines, 2-*endo*-hydroxy-4-*endo*-phenyl-5-azatricyclo[5.3.1.$0^{3,9}$]undecane (**6**) and the corresponding *N*-methyl derivative **7** in 34 and 49% yields, respectively.[17]

Synthesis of 2-*endo*-Hydroxy-5-azatricyclo[5.2.1.$0^{3,8}$]decane (15) and Related Derivatives via *N*-(*endo*-Bicyclo[2.2.1]hept-5-en-2-ylmethyl)nitrone (11). The reaction of benzaldehyde with hydroxylamine **10** prepared from 5-norbornene-2-carboxaldehyde (**9a**)[18] via oxime **9b** at room temperature in benzene afforded the nitrone **11a** (61%) (as a 95:5 endo–exo mixture from a 95:5 endo–exo mixture of **9a**). The intramolecular cycloaddition of **11a** occurred upon heating at 125 °C for 2 days in toluene to afford 4-*exo*-phenyl-5-aza-11-oxatetracyclo[5.2.1.$1^{2,5}$.$0^{3,8}$]undecane (**12a**) as colorless prisms in 67% yield after chromatography (silica gel–AcOEt) (Scheme II). The adduct **12a** was also obtained directly from **10** and benzaldehyde under the similar conditions in 44% yield. The assigned regio- and stereochemistry of **12a** were based on the ^1H NMR spectrum which revealed characteristic signals at δ 4.45 (, J = 6.0 Hz) and 4.00 (s) due to H_2 and H_4, respectively. The coupling constants of these signals were compatible with **12a** but not with regioisomer **13a**.[19] Treatment of **12a** with methyl iodide gave the methiodide **14a** which also showed a characteristic singlet at δ 5.75 due to H_4 and a triplet at δ 5.57 due to H_2, corroborating the given structure. X-ray structure analysis of **14a** provides unambiguous evidence to support the regio- and stereochemical assignment for the adduct **12a**. Usual reductive cleavage of **12a** with zinc in AcOH–H_2O under reflux gave 2-*endo*-hydroxy-4-*endo*-phenyl-5-azatricyclo[5.2.1.$0^{3,8}$]decane (**15a**) in 71% yield. ^1H NMR spectrum of **15a** revealed signals at δ 4.22 (dd, $J_{2,3}$ = 9.0, $J_{1,2}$ = 4.5 Hz) and 3.85 (s) due to H_2 and H_4, respectively, supporting the given structure.

Similarly, the reaction of **10** with paraformaldehyde in benzene at 90 °C for 90 h afforded directly the adduct **12b** (23%) after chromatography. The regiochemistry of **12b** was established by the following chemical conversions as well as NMR data. Appearance of two triplet resonances (for each 1C) assignable to C_4 and C_6 adjacent to the N atom at δ 59.4 and 56.6 in the ^{13}C NMR spectrum[14] and a characteristic triplet (J = 6.0 Hz) at δ 4.56 due to H_2 in ^1H NMR spectrum supported the shown **12b** structure rather than the regioisomer **13b**. Adduct **12b** gave methiodide **14b** which also had a characteristic triplet H_2 signal at δ 5.23 (J = 6.0 Hz). Reduction of **12b** with Zn–AcOH afforded **15b** (97%) which revealed a distinctive H_{2exo} signal at δ 4.19 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 4.5 Hz). The hydroxylamine **15b** was converted to 5-*p*-tosyl-5-azatricyclo[5.2.1.$0^{3,8}$]decane (**18**) via the hydroxy tosylamide **16** and the ketotosylamide **17** (Scheme II). ^{13}C NMR spectrum of **18** was comprised of six lines (3 d and 3 t) due to the skeletal nine carbons, attesting to the inherent C_s sym-

(11) For ^1H NMR data of isooxazolidines, see Furusaki, F.; Takeuchi, Y. in "Advances in Heterocyclic Chemistry"; Katritzky, A. R.; Boulton, A. J., Ed.; Academic Press: New York, 1977; Vol. 21, pp 238–240 and references cited therein.

(12) Examination of molecular models of **4** indicate that the CH–CH dihedral angles for H_3/H_2, H_3/H_9, and H_{12}/H_2 are 0°, 24°, and 105°, respectively; hence, the coupling constants calculated by the Karplus equation are 8.2, 6.8, and 0.3 Hz, respectively. These are close to the observed values. Cf also ref 13.

(13) For a general review on ^1H NMR spectroscopy, see: Jackman, L. M.; Sternhell, S. "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon: New York, 1969.

(14) (a) For ^{13}C NMR data of isooxazolidines, see ref 2. (b) For ^{13}C NMR of nonaromatic heterocyclic compounds, see: Eliel, E.; Pietrusiewicz, K. M. In "Topics in Carbon-13 NMR Spectroscopy"; Levy, G. C., Ed.; Wiley: New York, 1979; Vol. 3, Chapter 3. (c) For a general review on ^{13}C NMR, see: Breitmaier, E.; Voelter, W. "^{13}C NMR Spectroscopy", 2nd ed.; Verlag Chemie: Weinheim, 1978.

(15) A considerable steric repulsion between phenyl and H_{2endo} or H_{4endo} disfavors apparently the transition state for the *syn*-nitrone.

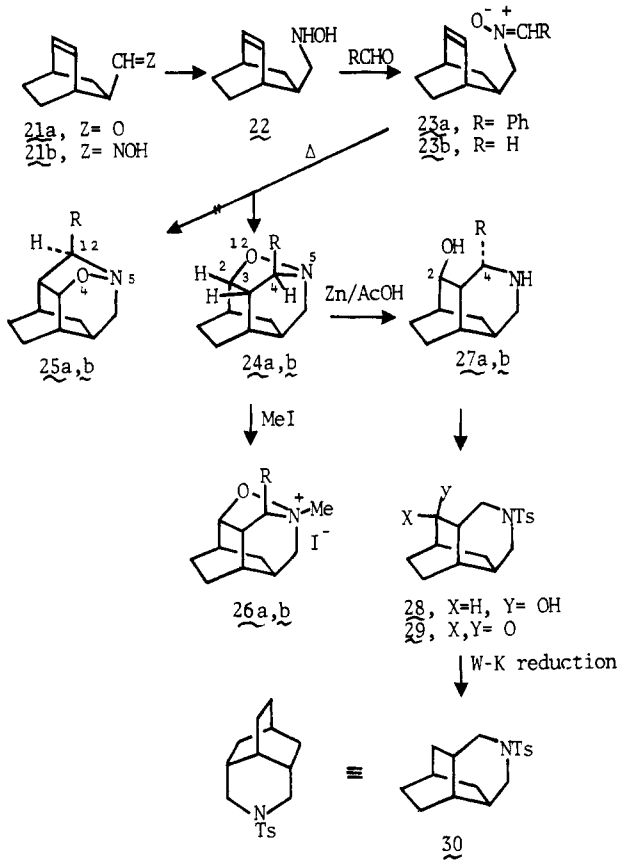
(16) For examples of intramolecular cycloaddition of *anti*- and *syn*-nitrones as well as their stereochemical discussions, see: (a) LeBel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc.* **1964**, *86*, 3759. (b) LeBel, N. A. Lajiness, T. A. *Tetrahedron Lett.* **1966**, 2173. (c) Reference 5a, p 125.

(17) For a general review on chemistry of isooxazolidines, see ref 11, pp 241–247.

(18) For a separation of endo and exo isomers by fractional distillation, see for example: (a) Freeman, P. K.; Desai, K. B. *J. Org. Chem.* **1971**, *36*, 1554. (b) Kampmeier, J. A.; Harris, S. H.; Wedegaertner, D. K. *Ibid.* **1980**, *45*, 315.

(19) The dihedral angles for H_2/H_1, H_2/H_3, and H_4/H_3 of **12a** are 25°, 25°, and 88°, respectively, corresponding to calculated coupling constants (Karplus equation) of 6.7, 6.7, and −0.3 Hz, respectively, while those for H_3/H_2, H_3/H_8, and H_{11}/H_2 of **13a** are 25°, 55°, and 108°, predicting the coupling constants of 6.7, 2.5, and 0.6 Hz, respectively.

Scheme III



metry of the molecule, and hence, the given regiochemistry of the intramolecular nitrone cycloadduct **12b**.

The observed regiospecific formation of **12** rather than **13** from **11** deserves some comments. Inspection of stereomodels assuming an *anti*-nitrone **11**[20] indicates clearly that a cyclic transition state **19a** leading to **12** suffers from only a minor geometrical constraint for an ideal parallel and simultaneous overlap of the nitrone moiety, whereas a transition state **20a** leading to **13** suffers from a considerable geometrical constraint as well as severe steric repulsion between nitrone H and H_{3endo}. Hence, the formation of **13** seems to be prohibitively difficult. In fact, even on heating **12a** at 150 °C for 2 days did not result in any formation of **13a**.

Synthesis of 2-*endo*-Hydroxy-5-azatricyclo-[5.3.1.0^{3,8}]undecane (27) and Related Derivatives via *N*-(*endo*-Bicyclo[2.2.2]oct-5-en-2-ylmethyl)nitrone (23). The reaction of benzaldehyde with hydroxylamine **22** prepared from bicyclo[2.2.2]oct-5-ene-2-carboxaldehyde (**21a**) (a 92:8 endo–exo mixture)[21] via oxime **21b** at room temperature afforded similarly the nitrone **23a** (36%). The intramolecular cycloaddition of **23a** occurred smoothly upon heating at 125 °C for 2 days in toluene to afford 4-*exo*-phenyl-5-aza-12-oxatetracyclo[5.3.1.1^{2,5}.0^{3,8}]dodecane (**24a**) as crystals (59%) after chromatography (Scheme III). The reaction of **22** with benzaldehyde at 125 °C also gave directly **24a** in 25% yield. The assigned structure was supported by the appearance of characteristic ^{1}H NMR signals at δ 4.15 (t, J = 6.0 Hz, H_2) and 4.02 (s, H_4). The adduct **24a** gave methiodide **26a** whose structure was determined by X-ray crystallographic analysis. The results confirmed also the structure of the intramolecular cycloadduct **24a** as assigned by NMR evidence. Reduction of **24a** with Zn–AcOH afforded 2-*endo*-hydroxy-4-*endo*-phenyl-5-azatricyclo[5.3.1.0^{3,8}]undecane (**27a**) (66%), whose NMR data were compatible with the given structure.[22]

Similarly the reaction of **22** with paraformaldehyde in benzene at 80 °C for 90 h gave adduct **24b** (49%) which gave the methiodide **26b** (96%). The assigned structures were evidenced by ^{1}H NMR signals at δ 4.33 (t, J = 6.0 Hz, H_2) of **24b** and 5.04 (t, J = 6.0 Hz, H_2) of **26b**, respectively. The regiochemistry was finally confirmed by the chemical conversion of **24b** to **30**. Usual Zn–AcOH reduction of **24b** gave the hydroxyamine **27b** in 66% yield. Treatment of **27b** with equimolar *p*-tosyl chloride in pyridine afforded **28** (75%) which was converted to the keto *p*-tosylamide **29** by PCC oxidation[23] (97%). Wolff–Kishner reduction of **29** afforded 5-*p*-tosyl-5-azatricyclo-[5.3.1.0^{3,8}]undecane (**30**).[24] The inherent C_s symmetry of **30** was evidenced by ^{13}C NMR spectrum which had seven lines (3 d and 4 t) assignable to the skeletal carbons.[25]

The regiospecific intramolecular cycloaddition of **23** is rationalized by the larger geometrical constraint and steric repulsion of a cyclic transition state **20b** compared to **19b**, similar to the nitrone **11** as discussed above.

Experimental Section

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained on a Jasco IRA-1 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol JNM-60HL instrument at 60 MHz and a Jeol JNM-60 FT NMR spectrometer at 15.04 MHz, respectively. Chemical shifts are reported in parts per million (δ) relative to Me_4Si as an internal standard, and coupling constants in hertz. Mass spectra were obtained with a Jeol JMS-D10 mass spectrometer at 75 eV. Microanalyses were performed with a Perkin-Elmer 240B elemental analyzer.

Bicyclo[3.2.1]oct-6-ene-3-*endo*-carboxaldehyde Oxime (1b). A mixture of the aldehyde **1a**[9] (272 mg, 2.00 mmol) and hydroxylamine hydrochloride (560 mg, 8.00 mmol) in pyridine (4 mL) was stirred at room temperature for 1 day. After neutralization with 10% hydrochloric acid, the mixture was extracted with chloroform (15 mL × 4) and the combined extracts were washed with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave an oily residue which was purified on a silica gel column (ether–*n*-hexane system) to afford the oxime **1b** as a colorless solid (221 mg, 73.2%): mp 68–69 °C; IR (KBr) 3220, 3080, 2940, 2870, 1650, 1460, 1360, 1300, 950, 920, 780, and 720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.0–7.8 (m, 1, D_2O exchangeable), 7.55 and 6.90 (both d, J = 6.0 Hz, 0.36 + 0.64),[26] 6.2–5.7 (m, 2), and 3.5–1.2 (m, 9).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.84; N, 9.14. Found: C, 79.92; H, 9.84; N, 8.86.

***N*-(*endo*-Bicyclo[3.2.1]oct-6-en-3-ylmethyl)hydroxylamine (2).** To a stirred mixture of the oxime **1b** (221 mg, 1.46 mmol) and a trace of bromocresol green in methanol (5 mL) was added $NaBH_3CN$ (200 mg, 3.18 mmol).[27] The resulting deep blue

(20) Both of two possible transition states of a *syn*-nitrone suffer from severe steric repulsions between R and NCH_2 or H_{3endo}.

(21) (a) Krantz, A.; Lin, C. Y. *J. Am. Chem. Soc.* **1973**, *95*, 5662. (b) Diels, O.; Alder, K.; Petersen, E.; Quebertz, F. *Liebigs Ann. Chem.* **1930**, *478*, 137.

(22) For ^{1}H NMR data of some related systems, see: (a) Aigami, K.; Inamoto, Y.; Takaishi, N.; Fujikura, Y. *J. Med. Chem.* **1976**, *19*, 536. (b) Whitlock, H. W., Jr.; Siefken, M. W. *J. Am. Chem. Soc.* **1968**, *90*, 4929. (c) Davalian, D.; Garratt, P. J.; Riguera, R. *J. Org. Chem.* **1977**, *42*, 368. (d) Moriarty, R. M.; Chien, C. C.; Adams, T. B. *Ibid.* **1979**, *44*, 2210. (e) Lickhart, R. W.; Kitadani, M.; Einstein, F. W. B.; Chow, Y. L. *Can. J. Chem.* **1978**, *56*, 2897. (f) Inokuma, S.; Katayama, S.; Ishizumi, K.; Katsube, J. *Heterocycles* **1983**, *20*, 13.

(23) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(24) For carbocyclic analogue, see: (a) Majerski, K. M.; Majerski, Z. *Tetrahedron Lett.* **1973**, 4915. (b) Krantz, A.; Lin, C. Y. *J. Chem. Soc., Chem. Commun.* **1971**, 1287.

(25) The regioisomer **25b** should be converted to 5-azatricyclo-[5.4.0.0^{3,9}]undecane (or trivial 5-aza-4-homoisotwistane) derivative of C_2 symmetry.

(26) These are assignable to CH=N of *syn*- and *anti*-oximes, respectively, of the endo isomer.

mixture was acidified by 2 N HCl–methanol with stirring to maintain the yellow color. After 1 h, the mixture was diluted with water (5 mL), basified with 20% KOH, saturated with sodium chloride, and extracted with chloroform (10 mL × 5). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The solid residue was crystallized from CH_2Cl_2–*n*-hexane to afford the hydroxylamine **2** as colorless crystals (170 mg, 76.1%): mp 76–77 °C; IR (KBr) 3270, 3060, 2940, 2880, 1500, 1460, 1420, 1360, 1260, 1010, 940, 920, 900, 800, 770, and 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.91 (s, 2), 5.65 (br s, 2, D_2O exchangeable), 2.97 (d, J = 6.5 Hz, 2), 2.48 (br s, 2), and 2.3–1.1 (m, 7).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.85; H, 9.84; N, 8.86.

12-*exo*-Phenyl-4-oxa-5-azatetracyclo[5.3.1.1^{2,5}.0^{3,9}]dodecane (4). A mixture of the hydroxylamine **2** (153 mg, 1.00 mmol), benzaldehyde (153 mg, 1.44 mmol), and 4A molecular sieves (0.6 g) in xylene (bp 138.5–141.5 °C, 3 mL) was heated under argon at reflux for 11 h. After removal of the solvent under reduced pressure, the residue was purified on a silica gel column (*n*-hexane–ether system) to afford the adduct **4** as crystals (from CH_2Cl_2–*n*-hexane) (229 mg, 95.0%), mp 85–86 °C. For spectral and analytical data, see Table I and II (supplementary material).

12-*exo*-Phenyl-4-oxa-5-methyl-5-azatetracyclo-[5.3.1.1^{2,5}.0^{3,9}]dodecane Iodide (5). Standing a solution of **4** (145 mg, 0.60 mmol) and methyl iodide (0.5 g, 3.52 mmol) in ether (5 mL) at ambient temperature for 5 days afforded crystalline precipitates which were filtered and washed with ether to give the methiodide **5** (207 mg, 90.0%), mp 190–193 °C dec. For characterization data, see Table I.

2-*endo*-Hydroxy-4-*endo*-phenyl-5-azatricyclo[5.3.1.0^{3,9}]-undecane (6). A mixture of **4** (145 mg, 0.60 mmol) and 10% Pd on carbon (100 mg) in EtOH (2 mL)–AcOH (0.1 mL) was stirred under an atmosphere of hydrogen at 20–25 °C for 10 days. After removal of the catalyst by filtration through Celite, the filtrate was evaporated to dryness under reduced pressure. The residue was purified on an alumina (Woelum N, Activity I) column eluting with ether to afford the hydroxyamine **6** as an oil (50 mg, 34.3%). For characterization data, see Table I.

2-*endo*-Hydroxy-4-*endo*-phenyl-5-methyl-5-azatricyclo-[5.3.1.0^{3,9}]undecane (7). To a stirred and ice-cooled mixture of $LiAlH_4$ (215 mg, 5.73 mmol) in anhydrous THF (20 mL) was added the methiodide **5** (170 mg, 0.44 mmol) under argon, and the mixture was heated to reflux for 1 day. The cooled mixture was carefully diluted with water (0.5 mL) and 10% NaOH (0.5 mL) and then dried (Na_2SO_4). Removal of the solvent gave an oil which was purified on an alumina column (*n*-hexane–ether system) to afford the hydroxyamine **7** as an oil (56 mg, 49.1%). For characterization data, see Table I.

Bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxaldehyde Oxime (9b). A mixture of 5-norbornene-2-carboxaldehyde (**9a**) (a 95:5 endo–exo mixture[18] was used, 2.50 g, 20.5 mmol) and hydroxylamine hydrochloride (5.70 g, 82.0 mmol) in pyridine (7 mL) was stirred at ambient temperature for 3 h. The mixture was diluted with ice–water (5 mL) and chloroform (5 mL). The organic layer was separated and washed with 1% HCl, water, 3% $NaHCO_3$, and saturated sodium chloride aqueous solution, successively, and dried (Na_2SO_4). Removal of the solvent and two Kugelrohr distillations at 85–90 °C under 0.5 mmHg gave the oxime **9b** as a colorless oil (2.30 g, 81.8%): IR (neat) 3220, 3050, 2960, 2860, 1655, 1445, 1335, 995, 930, and 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.7 (br s, 1, D_2O exchangeable), 7.46 and 6.73 (both d, J = 7.0 Hz, 0.02 + 0.02),[28] 7.07 and 6.37 (both d, J = 7.5 Hz, 0.51 + 0.45),[26] 6.5–5.4 (m, 2), 3.7–2.7 (m, 3), 2.3–1.2 (m, 3), and 1.2–0.7 (AB type m, 0.96).[29]

Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.02; H, 8.19; N, 10.12.

***N*-(*endo*-Bicyclo[2.2.1]hept-5-en-2-ylmethyl)hydroxylamine (10).** The oxime **9b** (0.50 g, 3.64 mmol) was reduced with $NaBH_3CN$ (0.49 g, 7.80 mmol) in MeOH (10 mL) at room temperature for 1 h under acidic conditions (bromocresol green/2 N HCl–MeOH) as above. Usual workup gave crude hydroxylamine **10** as an oil (0.50 g, 98.6%), which was used for the next step without further purification: IR (neat) 3270, 3060, 2970, 2870, 1640, 1445, 1340, 1250, 1030, 830, 820, and 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.43 (br s, 2, D_2O exchangeable), 6.45–5.80 (m, 2), and 3.8–0.4 (m, 9).

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.23; H, 9.21; N, 9.88.

***C*-Phenyl-*N*-(*endo*-bicyclo[2.2.1]hept-5-en-2-ylmethyl)-nitrone (11a).** A mixture of the hydroxylamine **10** (140 mg, 1.00 mmol), benzaldehyde (130 mg, 1.23 mmol), and 4A molecular sieves (0.5 g) in benzene (5 mL) was stirred for 2 h at room temperature. The molecular sieves were filtered and washed with benzene. The combined filtrate and washings were evaporated under reduced pressure. The residual oil was purified on a preparative TLC of silica gel (Wako gel C-200, AcOEt) to afford the nitrone **11a** as a colorless oil (ca. 95:5 endo–exo mixture) (140 mg, 61.2%): IR (neat) 3060, 2980, 2950, 2880, 1590, 1570, 1450, 1430, 1140, 940, 780, 730, and 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.4–7.2 (m, 6), 6.4–5.9 (m, 2), 3.94 and 3.64 (both d, J = 7.5 Hz, 0.10 + 1.90),[30] 3.2–1.2 (m, 6), and 0.65 (m, 0.95).[29]

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.09; H, 7.66; N, 6.21.

4-*exo*-Phenyl-5-aza-11-oxatetracyclo[5.2.1.1^{2,5}.0^{3,8}]undecane (12a). A. From 11a. A solution of **11a** (90 mg, 0.40 mmol) in toluene (2 mL) was heated under argon in a sealed tube at 125 °C for 2 days. Removal of the solvent gave an oily residue which was purified on a preparative TLC (silca gel, AcOEt) to afford the nitrone cycloadduct **12a** as crystals (from methanol) (60 mg, 66.7%), mp 107–109 °C. For spectral and analytical data, see Table I and II.

B. From 10 and Benzaldehyde. A mixture of **10** (70 mg, 0.50 mmol), benzaldehyde (70 mg, 0.66 mmol), and 4A molecular sieves (0.5 g) in toluene (3 mL) was heated at 125 °C under argon in a sealed tube for 1 week. Usual workup as above and preparative TLC (silica gel, AcOEt) gave the adduct **12a** (50 mg, 44.0%).

5-Aza-11-oxatetracyclo[5.2.1.1^{2,5}.0^{3,8}]undecane (12b). A mixture of **10** (610 mg, 4.38 mmol), paraformaldehyde (600 mg), and 4A molecular sieves (1.5 g) in benzene (10 mL) was heated under argon in a sealed tube at 90 °C for 4 days. After removal of the molecular sieves, the solvent was removed under reduced pressure. The oily residue was chromatographed on a silica gel column eluting with AcOEt–$CHCl_3$ (1:1 v/v) to afford the adduct **12b** as crystals (CH_2Cl_2–*n*-hexane) (160 mg, 22.8%), mp 180–182 °C. For characterization data, see Table I and II.

5-Methyl-4-*exo*-phenyl-5-aza-11-oxatetracyclo-[5.2.1.1^{2,5}.0^{3,8}]undecane Iodide (14a). A solution of **12a** (50 mg, 0.22 mmol) in methyl iodide (1.14 g, 8.03 mmol) and CH_2Cl_2 (0.5 mL) was allowed to stand at ambient temperature for 3 days. The resulted crystalline precipitates were filtered and washed with acetone to give the methiodide **14a** (80 mg, 98.8%), mp 170–171 °C dec. For characterization data, see Table I.

5-Methyl-5-aza-11-oxatetracyclo[5.2.1.1^{2,5}.0^{3,8}]undecane Iodide (14b). The adduct **12b** (60 mg, 0.40 mmol) was treated with MeI (1.14 g, 8.03 mmol) in CH_2Cl_2 (0.5 mL) similarly as above. The resulted crystals were filtered and washed with acetone to give the methiodide **14b** (100 mg, 86.2%), mp 230 °C dec. For characterization data, see Table I.

2-*endo*-Hydroxy-4-*endo*-phenyl-5-azatricyclo[5.2.1.0^{3,8}]-decane (15a). A stirred mixture of the adduct **12a** (70 mg, 0.31 mmol) and zinc dust (0.5 g) in AcOH (1 mL) and water (0.5 mL) was heated to reflux for 6 h. The cooled mixture was basified with 20% aqueous KOH and extracted with $CHCl_3$ (10 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residual solid was crystallized from CH_2Cl_2–*n*-hexane to afford **15a** as crystals (50 mg, 70.8%), mp 98–99 °C. For characterization data, see Table I and II.

2-*endo*-Hydroxy-5-azatricyclo[5.2.1.0^{3,8}]decane (15b). The adduct **12b** (120 mg, 0.79 mmol) was reduced with zinc dust (0.9 g) in AcOH (1.5 mL) and water (0.5 mL) under reflux for 6.5 h. The workup as above and crystallization from CH_2Cl_2–*n*-hexane gave **15b** as crystals (118 mg, 97.0%), mp 94–97 °C. For characterization data, see Table I and II.

(27) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(28) These are due to CH=N of *syn*- and *anti*-oximes of the exo isomer.

(29) This signal is due to H_{3n} of the endo isomer.

(30) These are assignable to CH_2N of *exo*- and *endo*-nitrones.

2-*endo*-Hydroxy-5-*p*-tosyl-5-azatricyclo[5.2.1.0^{3,8}]decane (16). To a stirred and ice-cooled mixture of *p*-toluenesulfonyl chloride (170 mg, 0.89 mmol) in anhydrous pyridine (5 mL) was added the hydroxyamine **15b** (170 mg, 0.89 mmol). After the stirring was continued at room temperature for 15 h, the mixture was diluted with water and extracted with $CHCl_3$ (10 mL × 3). The combined extracts were washed successively with water, 2% HCl, and water and dried ($MgSO_4$). Removal of the solvent and chromatography on a short silica gel column ($CHCl_3$) afforded the tosyl amide **16** as crystals (CH_2Cl_2–*n*-hexane) (240 mg, 87.6%), mp 130–131 °C. For characterization data, see Table I and II.

5-*p*-Tosyl-5-azatricyclo[5.2.1.0^{3,8}]decan-2-one (17). A mixture of **16** (240 mg, 0.78 mmol) and PCC[23] (260 mg, 1.21 mmol) in anhydrous CH_2Cl_2 (6 mL) was stirred at room temperature for 3 h. The mixture was filtered through a short silica gel column ($CHCl_3$). Removal of the solvent and crystallization from CH_2Cl_2–*n*-hexane gave the ketone **17** as crystals (150 mg, 62.9%). For characterization data, see Table I and II.

5-*p*-Tosyl-5-azatricyclo[5.2.1.0^{3,8}]decane (18). A mixture of **17** (140 mg, 0.46 mmol), hydrazine hydrochloride (60 mg, 0.57 mmol), and 100% hydrazine hydrate (250 mg, 5.00 mmol) in diethylene glycol (10 mL) was refluxed for 2.5 h. To the cooled mixture was added potassium hydroxide (250 mg) and the mixture was concentrated until the temperature rose to 230 °C and refluxed for 4.5 h. The cooled mixture was diluted with water and extracted with ether (10 mL × 4). The combined extracts were washed with water, 5% HCl, and water successively, and dried (Na_2SO_4). Removal of the solvent and chromatography (silica gel, CH_2Cl_2) afforded the tosylazahomobrendane **18** as crystals (CH_2Cl_2–*n*-hexane) (40 mg, 29.9%), mp 125–127 °C. For spectral and analytical data, see Table I and II.

Bicyclo[2.2.2]oct-5-ene-2-*endo*-carboxaldehyde Oxime (21b). A mixture of bicyclo[2.2.2]oct-5-ene-2-*endo*-carboxaldehyde (**21a**)[21] (a 92:8 endo–exo mixture was used, 1.87 g, 13.7 mmol) and hydroxylamine hydrochloride (4.80 g, 69.1 mmol) in pyridine (5 mL) was stirred at ambient temperature for 3 h. Workup as above and Kugelrohr distillation at 90–93 °C under 0.5 mmHg gave the oxime **21b** as a colorless oil which solidified on standing (1.30 g, 62.8%): mp 40–43 °C; IR (neat) 3600–2400, 3030, 2930, 2860, 1645, 1450, 1300, 940, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.80 (br s, 1, D_2O exchangeable), 7.48 and 6.80 (both d, J = 6.5 Hz, ca. 0.04 + 0.04),[28] 7.13 and 6.43 (both d, J = 7.5 Hz, ca. 0.51 + 0.41),[26] 6.6–6.0 (m, 2), 3.5–2.6 (m, 3), and 2.3–1.0 (m, 6).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.27. Found: C, 71.75; H, 8.68; N, 9.32.

***N*-(*endo*-Bicyclo[2.2.2]oct-5-en-2-ylmethyl)hydroxylamine (22).** The oxime **21b** (1.28 g, 8.37 mmol) was reduced with $NaBH_3CN$ (1.50 g, 23.9 mmol) in MeOH (10 mL) for 1 h as above. Usual workup gave the hydroxylamine **22** as an oil which was used for the next step without further purification (1.20 g, 93.5%): IR (neat) 3600–2400, 3030, 2930, 2860, 1450, 1375, 1030, 1010, and 700 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.80 (br s, 2, D_2O exchangeable), 6.5–6.0 (m, 2), 3.1–2.3 (m, 2), and 2.2–0.9 (m, 9).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.50; H, 9.95; N, 9.24.

***C*-Phenyl-*N*-(*endo*-bicyclo[2.2.2]oct-5-en-2-ylmethyl)-nitrone (23a).** A mixture of **22** (77 mg, 0.50 mmol), benzaldehyde (74 mg, 0.70 mmol), and 4A molecular sieves (0.5 g) in benzene (3 mL) was stirred at room temperature for 15 h. The workup as above and preparative TLC (Wako gel C-200, $CHCl_3$–AcOEt 1:1 v/v) gave the nitrone **23a** as an oil (this material was a ca. 80:20 mixture of endo and exo isomers) (43 mg, 35.6%): IR (neat) 3045, 2940, 2860, 1580, 1570, 1455, 1425, 1160, 760, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.4–7.2 (m, 6), 6.6–6.0 (m, 2), 3.95 and 3.60 (both br d, J = ca. 7.5 Hz, 0.4 + 1.6),[30] 3.0–2.3 (m, 3), and 2.3–0.6 (m, 6).

4-*exo*-Phenyl-5-aza-12-oxatetracyclo[5.3.1.1^{2,5}.0^{3,8}]dodecane (24a). A. From 23a. A solution of **23a** (35 mg, 0.14 mmol) in toluene (0.5 mL) was heated under argon in a sealed tube at 125 °C for 2 days. Removal of the solvent under reduced pressure and preparative TLC (Merck, Kieselgel 60 F-254, $CHCl_3$) afforded **24a** as crystals (CH_2Cl_2–*n*-hexane) (20 mg, 59.2%), mp 71–74 °C. For characterization data, see Table I and II.

B. From 22 and Benzaldehyde. A mixture of **22** (510 mg, 3.31 mmol), benzaldehyde (500 mg, 4.71 mmol), and 4A molecular sieves (1.5 g) in benzene (5 mL) was heated under argon in a sealed tube at 100 °C for 6 days. Usual workup as above and chromatography on a silica gel column ($CHCl_3$) gave **24a** (200 mg, 25.1%).

5-Aza-12-oxatetracyclo[5.3.1.1^{2,5}.0^{3,8}]dodecane (24b). A mixture of **22** (1.30 g, 8.37 mmol), paraformaldehyde (1.70 g), and 4A molecular sieves (1.5 g) in benzene (20 mL) was heated under argon at 80 °C for 5 days in a sealed tube. The workup as above and chromatography (silica gel, $CHCl_3$) gave the adduct **24b** as colorless crystals (CH_2Cl_2–*n*-hexane) (680 mg, 49.0%), mp 133–136 °C. For characterization data, see Table I and II.

4-*exo*-Phenyl-5-methyl-5-aza-12-oxatetracyclo-[5.3.1.1^{2,5}.0^{3,8}]dodecane Iodide (26a). A solution of **24a** (50 mg, 0.21 mmol) in MeI (1.14 g, 8.03 mmol) and CH_2Cl_2 (0.3 mL) was allowed to stand at ambient temperature for 1 week. The resulted crystalline precipitates were filtered and washed with ether to give the methiodide **26a** (80 mg, 99.4%), mp 162–165 °C dec.. For characterization data, see Table I.

5-Methyl-5-aza-12-oxatetracyclo[5.3.1.1^{2,5}.0^{3,8}]dodecane Iodide (26b). The adduct **24b** (180 mg, 1.09 mmol) was treated with MeI (1.14 g, 8.03 mmol) in CH_2Cl_2 (0.5 mL) for 4 days as above. The resulted crystals were filtered and washed with ether to give the methiodide **26b** (320 mg, 95.6%), mp 190 °C dec. For characterization data, see Table I.

2-*endo*-Hydroxy-4-*endo*-phenyl-5-azatricyclo[5.3.1.0^{3,8}]-undecane (27a). The adduct **24a** (150 mg, 0.62 mmol) was reduced with zinc dust (1.0 g) in AcOH (2 mL) and water (1 mL) under reflux for 6 h. The usual workup with 20% aqueous KOH and extraction with $CHCl_3$ gave **27a** as crystals after crystallization from CH_2Cl_2–*n*-hexane (100 mg, 66.1%), mp 159–161 °C. For characterization data, see Table I and II.

2-*endo*-Hydroxy-5-azatricyclo[5.3.1.0^{3,8}]undecane (27b). The adduct **24b** (90 mg, 0.54 mmol) was reduced with zinc dust (0.5 g) in AcOH (2 mL) and water (1 mL) under reflux for 6 h. Usual workup as above and crystallization from CH_2Cl_2–*n*-hexane afforded **27b** as crystals (60 mg, 66.4%), mp 43–45 °C. For characterization data, see Table I and II.

2-*endo*-Hydroxy-5-*p*-tosyl-5-azatricyclo[5.3.1.0^{3,8}]undecane (28). The hydroxyamine **27b** (55 mg, 0.33 mmol) was treated with *p*-toluenesulfonyl chloride (65 mg, 0.34 mmol) in pyridine (4 mL) under ice cooling for 15 h as above. The usual workup and chromatography (silica gel, $CHCl_3$) gave the tosyl amide **28** as crystals (CH_2Cl_2–*n*-hexane) (80 mg, 75.4%), mp 138–139 °C. For characterization data, see Table I and II.

5-*p*-Tosyl-5-azatricyclo[5.3.1.0^{3,8}]undecan-2-one (29). A mixture of **28** (65 mg, 0.20 mmol) and PCC (50 mg, 0.23 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 2 h. The mixture was directly filtered through a short silica gel column with $CHCl_3$. Concentration of the solvent and dilution with *n*-hexane gave the ketone **29** as crystals (62 mg, 97.1%), mp 157–158 °C. For characterization data, see Table I and II.

5-*p*-Tosyl-5-azatricyclo[5.3.1.0^{3,8}]undecane (30). A mixture of **29** (610 mg, 1.91 mmol), hydrazine hydrochloride (250 mg, 2.37 mmol), and 100% hydrazine hydrate (1.00 g, 20 mmol) in diethylene glycol (24 mL) was heated to reflux for 5 h. After addition of potassium hydroxide (0.6 g), the mixture was concentrated until the temperature rises to 230 °C and refluxed for 5 h. The workup as above and chromatography (silica gel, CH_2Cl_2) afforded **30** as crystals (CH_2Cl_2–*n*-hexane) (210 mg, 36.0%), mp 125–127 °C. For spectral data, see Table I and II.[31]

Supplementary Material Available: Table I (IR, ^{1}H NMR, mass spectra, and C, H, N analyses for compounds **4–7**, **12a,b**, **14a,b**, **15a,b**, **16–18**, **24a,b**, **26a,b**, **27a,b**, **28–30**), Table II (^{13}C NMR data of **4**, **12a,b**, **15a,b**, **16–18**, **24a,b**, **27a,b**, and **28–30**), crystal data and analytical methods of the methiodides **14a** and **26a**, Figures 1–4 (ORTEP and stereodrawings of X-ray crystallographically determined structures of **14a** and **26a**), and Tables III–V and VI–VIII (listing of atomic parameters, thermal parameters, selected bond lengths, and bond angles for **14a** and **26a**, respectively) (15 pages). Ordering information is given in any current masthead page.

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